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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/980,645	ANKER ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,17,21,25-27,78 and 88* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 17, 21, 25-27, 78 and 88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-2, 17, 21, 25-27, 78 and newly added 88 are pending and are being acted in this Office Action.

2. In view of the amendment filed 11/19/07, the following rejections remain.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claim 78 stands rejected under 35 U.S.C. 102(b) as being anticipated by Larghi et al (of record, Aliment Pharmacol Ther 11(2): 409-14, April 1997; PTO 892) as evidenced by US Pat No 4,337,206 (issued 29, 1982; PTO 892).

Larghi et al *et al* teach a formulation comprising diuretics such as ursodeoxycholic acid and tauro-ursodeoxycholic acid (see entire document, abstract, page 410, col. 1, last paragraph, in particular). A composition is a composition, irrespective of its intended use. Evidentiary reference '206 patent teaches ursodeoxycholic acid is used as a diuretic (see col. 1, line 10-17, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 11/19/07 have been fully considered but are not found persuasive.

Applicants' position is that claim 78 requires a pharmaceutical composition comprising ursodeoxycholic acid and a diuretic. Since neither ursodeoxycholic acid nor tauro-ursodeoxycholic is known as a diuretic, Larghi does not teach all of the limitations of the present invention.

Contrary to applicant's assertion that ursodeoxycholic is not known as a diuretic, enclosed here is evidentiary reference US Pat No 4,337,206 that discloses ursodeoxycholic has been used as a diuretic (see col. 1, lines 10-17, in particular). Larghi et al *et al* teach a formulation comprising diuretics such as ursodeoxycholic acid and tauro-ursodeoxycholic acid (see entire document, abstract, page 410, col. 1, last paragraph, in particular). A composition is a

composition, irrespective of its intended use. Thus, the reference teachings anticipate the claimed invention.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-2, 17, and 25-27 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Anker et al (of record, Am J Cardiology 79: 1426-1430, 1997; PTO 1449) in view of US 5,674,855 (of record, Oct 7, 1997; PTO 892) and Gennaro et al (of record, in Remington: The science and practice of Pharmacy, pages 710-713, Mach publishing company, Eston, Pennsylvania 18042, 1995; PTO 892).

Anker et al teach human patients with chronic heart failure (CHF) such as idiopathic dilated cardiomyopathy exhibit immune activation as measured by a significant elevated level of soluble CD14 receptor (LPS receptor) as compared to control, see page 1427, Table 1, Figure 2, in particular), especially in those with cachexia. These CHF patients also have increase levels of TNF-α due to endotoxin (LPS) interacting with monocytes, see page 1428, col. 2, second paragraph, in particular). Anker et al teach a method detecting the levels of TNF-α and soluble CD14 using commercially available ELISA test kits, see page 1427, col. 1, in particular).

The invention in claim 1 differs from the teachings of the reference only in that the method for ameliorating or treating endotoxin-mediated TNF-α production in acute or chronic heart failure in a human by administering ursoedoxycholic acid if any of the TNF-α, soluble CD14 or LPS is elevated.

The invention in claim 25 differs from the teachings of the reference only in that method wherein the bile acid is administered orally.

The invention in claim 27 differs from the teachings of the reference only in that the method wherein the bile acid is administered rectally.

The '855 patent teaches a method of treating endotoxin LPS mediated immune activation such as TNF-α production (inflammatory cytokine production) by administering to a subject such as a human (see col. 9, line 44, in particular) a therapeutically effective amount of ursodeoxycholic acid (see col. 6, line 38-41, col. 7, lines 47-49, col. 8, lines 1-7, col. 8, lines 31-34, col. 9, lines 14-21, in particular). The '855 patent teaches such composition is useful in treating endotoxemia (see col. 11, lines 1-2, in particular). The reference ursodeoxycholic acid can be administered alone or in combination with other phospholipid (see col. 9, lines 57-67, in particular). The reference ursodeoxycholic acid is administered intravenously (see col. 8, line 39, in particular).

Gennaro et al teach oral route is the most convenient route for access to the systemic circulation (see page 710, col. 1, last paragraph, in particular) and rectal route is used quite frequently in and important ways of administrating a drug in pediatrics and geriatrics (see page 710, paragraph bridging col. 1 and 2, in particular). The route of administration such as rectally, or orally is within the purview of one of ordinary skill in the pharmaceutical art as taught by Gennaro et al.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer to a human subject having chronic heart failure with elevated TNF-α production or soluble CD14 receptor as taught by Anker et al a therapeutically effective amount of ursodeoxycholic acid alone via intravenously as taught by the '855 patent or is administered orally or rectally as taught by Gennaro et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Gennaro et al teach oral route is the most convenient route for access to the systemic circulation (see page 710, col. 1, last paragraph, in particular) while rectal route is used quite frequently in and important ways of administrating a drug in pediatrics and geriatrics as taught by Gennaro et al (see page 710, paragraph bridging col. 1 and 2, in particular). The route of administration is within the purview of one of ordinary skill in the pharmaceutical art. One having ordinary skill in the art would have been motivated to do administer ursodeoxycholic acid as a method of treating endotoxin-mediated immune activation because the '855 patent teaches ursodeoxycholic acid is useful in treating endotoxemia by inhibiting inflammatory cytokine TNF-α production caused by endotoxin LPS (see col. 11, lines 1-2, in particular). Anker et al teach human patients with chronic heart failure (CHF) such as idiopathic dilated cardiomyopathy has significant elevated level of soluble CD14 receptor (LPS receptor) or TNF-α due to endotoxin (LPS) (see entire document, see page 1427, Table 1, Figure 2, page 1428, col. 2, second paragraph, in particular).

Applicants' arguments filed 11/19/07 have been fully considered but are not found persuasive.

Applicants' position is that the '855 patent fails to teach a definition of endotoxemia. Webster' s dictionary defines "endotoxemia" as 'the presence of endotoxins in the blood'. It is not clear that the presence of *any* amount of endotoxins represents a medical condition in need of treatment, nor is there any guidance about what constitutes treatment. Thus, in the context of the '855 patent, the term "treatment of endotoxemia" is meaningless. Indeed, an approved diagnostic test for endotoxemia was not available at the time of the application, thus making any assessment for treatment unclear. Moreover, the '855 patent refers to endotoxemia only in the context of Gram-negative bacterial endotoxic shock, which is unrelated to heart failure. Accordingly, the '855 patent is It is well known by those of ordinary skill in the art that endotoxin produces multiple biochemical effects. Such effects include:

1) Production of cytokines, including IL-1, IL-6, IL-8, tumor necrosis factor (TNF) and platelet-activating factor (PAF);

2) Activation of the complement cascade (C3a and C5a cause histamine release, and effect chemotaxis and accumulation, leading to inflammation);

3) Activation of the coagulation cascade. Initial activation of the Hageman factor can activate several humoral systems resulting in coagulation leading to thrombosis and internal bleeding, activation of the complement alternative pathway, plasmin

activation leading to fibrinolysis and hemorrhaging, and kinin activation resulting in hyptension.

Ultimately, one or a combination of the foregoing effects leads to death. It is also known that not all of these biochemical effects result from similar levels of endotoxin, that multiple cells and multiple locations are involved.

Example 9 of the '855 patent is the only example where bile acids are studied, and shows only an effect on death and only with sodium cholate. There is absolutely no disclosure that any bile acids are effective on any particular end points other than death as a result of endotoxins. Furthermore, there is no suggestion in the '855 patent as to which of the many biochemical pathways listed above are affected by sodium cholate and which are not.

Moreover, the '855 patent is also silent as to whether TNF-α was even involved in endotoxin induced death (in other words, whether a reduction in TNF-ct production would cause a concomitant reduction in lethality. This is particularly relevant given the very high levels of endotoxin used. Consider that Example 9 of the '855 patent uses a dose of 40 mg/kg of LPS, which is a much higher does than the amount used for lethality studies in prior experiments (see col. 9, lines 7-8). Thus, there is a clear separation between the levels of endotoxin used in example 9 as compared to the other examples in the '855 patent. By comparison, the levels of endotoxin the present application are well below those otherwise seen (see page 38, lines 15-16 of the present application).

The applicants therefore submit that the '855 patent is not enabled for the treatment of *any* endotoxin or, contrarily, is not enabled for the treatment of endotoxemia in the context of heart failure, which involves levels of endotoxins far less than those that produce endotoxic shock. Accordingly, the skilled artisan would not be motivated to combine the teachings of the cited references to achieve the method of the present invention, and a *primafacie* case of obviousness cannot be established. The applicants respectfully request that the Examiner withdraw these rejections.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, the teachings of Anker et al pertaining to the increase levels of TNF-α, endotoxin LPS, and soluble CD14 in

patient associated with heart failure, and the teachings of the '855 patent indicating success in reducing TNF-α mediated by endotoxin LPS and death associated with endotoxin LPS in patient by administering bile acid ursodeoxycholic acid would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144.

Contrary to applicants' assertion that diagnostic test for endotoxemia was not available at the time of the application, Anker et al teach a method detecting the levels of TNF-α and soluble CD14 using commercially available ELISA test kits, see page 1427, col. 1, in particular). Anker et al teach human patients with chronic heart failure (CHF) such as idiopathic dilated cardiomyopathy exhibit immune activation as measured by a significant elevated level of soluble CD14 receptor (LPS receptor) as compared to control, see page 1427, Table 1, Figure 2, in particular), especially in those with cachexia. These CHF patients also have increase levels of TNF-α due to endotoxin (LPS) interacting with monocytes, see page 1428, col. 2, second paragraph, in particular).

The '855 patent teaches endotoxin LPS-mediated stimulation of TNF-α (col. 5, line 13-15, Figure 9, open bar, in particular). The '855 patent teaches TNF-α production was substantially reduced with phospholipid PC (see col. 7, lines 18-20, Figures 8-9, in particular). The '855 patent teaches a method of treating endotoxin LPS mediated immune activation such as TNF-α production (inflammatory cytokine production) by administering to a subject such as a human (see col. 9, line 44, in particular) a therapeutically effective amount of ursodeoxycholic acid (see col. 6, line 38-41, col. 7, lines 47-49, col. 8, lines 1-7, col. 8, lines 31-34, col. 9, lines 14-21, in particular). The '855 patent teaches ursodeoxycholic acid is useful in treating endotoxemia (see col. 11, lines 1-2, in particular). The reference ursodeoxycholic acid can be administered alone or in combination with other phospholipid (see col. 9, lines 57-67, in particular). The reference ursodeoxycholic acid is administered intravenously (see col. 8, line 39, in particular).

With respect to the argument that the '855 patent refers to endotoxemia only in the context of Gram-negative bacterial endotoxic shock, which is unrelated to heart failure, The '855

patent teaches Gram-negative bacteria shock involved endotoxin LPS that stimulates TNF-α in the subject (see col. 2, lines 45-65, col. 5, lines 11-15, Figures 8-9, in particular). Although the '855 patent does not teach TNF-α associated with teach heart failure, Anker et al teach human patients with chronic heart failure (CHF) such as idiopathic dilated cardiomyopathy exhibit a significant elevated level of soluble CD14 receptor (LPS receptor) as compared to control, see page 1427, Table 1, Figure 2, in particular), especially in those with cachexia. These CHF patients also have increase levels of TNF-α due to endotoxin (LPS) interacting with monocytes, see page 1428, col. 2, second paragraph, in particular).

With respect to argument that the '855 patent is not enabled for the treatment of *any* endotoxin, every patent is presumed to be valid and operable (35 U.S.C 282), see *Metropolitan Eng. Co. v. Coe*, 78 F.2d 199, 25 USPQ 216 (D.C.Cir. 1935), MPEP 716.07. The '855 patent teaches administering bile acid ursodeoxycholic acid to a subject to reduce endotoxin LPS mediated endotoxemia such as increase in TNF-α, endotoxic shock, also known as cachexia and death (see col. 9, line 44, col. 6, line 38-41, col. 7, lines 47-49, col. 8, lines 1-7, col. 8, lines 31-34, col. 9, lines 14-21, in particular).

8. Claim 21 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Anker et al (of record, Am J Cardiology 79: 1426-1430, 1997; PTO 1449) in view of US 5,674,855 (of record, Oct 7, 1997; PTO 892) and Gennaro et al (of record, in Remington: The science and practice of Pharmacy, pages 710-713, Mach publishing company, Eston, Pennsylvania 18042, 1995; PTO 892) as applied to claims 1-2, 17, are 25-27 mentioned above and further in view of Schwarzenberg et al (of record, Pediatr Res 35 (2): 214-217, Feb1994; PTO 892).

The combined teachings of Anker et al, the '855 patent, and Gennaro et al have been discussed supra.

The claimed invention in claim 21 differs from the combined teachings of the references only in that the method for ameliorating or treating endotoxin-mediated TNF-α production in acute or chronic heart failure in a human by administering ursodeoxycholic acid wherein the ursodeoxycholic acid is able to reduce the permeability of the gut wall to bacteria and/or endotoxin (lipopolysaccharide, LPS).

Schwarzenberg et al teach LPS can cross the intestinal barrier (gut wall) and administration of ursodeoxycholic acid (UDCA) can decrease the translocation of LPS and prevent the cytokine response as measured by TNF levels (see abstract, in particular). Schwarzenberg et al teach UDCA administered prophylactically might reduce the morbidity in clinical conditions leading to gut-derived endotoxemia (see abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer to a human subject having chronic heart failure with elevated TNF-α production or soluble CD14 receptor as taught by Anker et al a therapeutically effective amount of ursodeoxycholic acid as taught by the '855 patent or Schwarzenberg et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because ursodeoxycholic acid (UDCA) can decrease the translocation of LPS and prevent the cytokine response as measured by TNF levels as taught by Schwarzenberg et al (see abstract, in particular).

Claim 21 stands rejected for the reasons of record.

9. The following new grounds of objection and rejections are necessitated by the amendment filed 11/19/07.

10. Newly added claim 88 is objected to because of typographical error "concentration **or** ursodeoxycholic acid". The word "or" should have been "of".

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

12. Claim 88 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is: what is being administering to the patient to increase the concentration of ursodeoxycholic acid? Further, claim 88 is incomplete for failing to achieve the goal set forth in the preamble.

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 1-2, 17, 21, and 25-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) measuring the any level such as tissue level of TNF-α, endotoxin or soluble CD14 for the claimed method of ameliorating or treating endotoxin-mediated TNF-α in acute or chronic heart failure in a human patient. (2) a method for ameliorating or treating endotoxin mediated TNF-α prodction in acute and chronic heart failure comprising the step of increasing the concentration of ursodeoxycholic acid in the blood of a patient.

Claim 1 and dependent claims therefrom encompass a method for ameliorating or treating endotoxin-mediated TNF-α in acute or chronic heart failure in a human patient by measuring tissue level as well as plasma levels of TNF-α, endotoxin or soluble CD14 in human patient with acute or chronic heart failure and if such level is elevated, administering to the patient with a ursodeoxycholic acid, or ursodeoxycholic acid in combination with diuretics.

Newly added claim 88 encompasses a method for ameliorating or treating endotoxin mediated TNF-α production in acute and chronic heart failure comprising the step of increasing the concentration of ursodeoxycholic acid in the blood of a patient without the active step that is required to increase the concentration of ursodeoxycholic acid.

The specification at page 31, lines 1-3 discloses only measuring *plasma levels* of TNF-α, endotoxin or soluble CD14 in patients with chronic heart failure with or without peripheral edema. The specification at page 7 discloses administering a diuretic with ursodeoxycholic to the patient.

The specification does not disclose measuring *tissue levels* of TNF-α, endotoxin or soluble CD14 in human patient with acute or chronic heart failure. The specification does not

disclose administering to the patient with ursodeoxycholic acid in combination with *multiple* diuretics.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

Adequate written description requires more than a mere statement that it is part of the invention. The antagonist itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provides only the bovine sequence. With the exception of measuring the *plasma level* of TNF-α, endotoxin or soluble CD14 in patients with chronic heart failure with or without peripheral edema, there is insufficient written description about measuring tissue level of TNF-α, endotoxin or soluble CD14 in patients with chronic heart failure with or without peripheral edema for the claimed method. Therefore, only measuring plasma level of TNF-α, endotoxin or soluble CD14 meet the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

15. Claim 88 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is new matter.**

The recitation of "the step of *increasing the concentration of ursodeoxycholic acid in the blood of a patient*" in claim 88 represents a departure from the specification and the claims as originally filed. Applicants have not point out the support in the amendment filed 11/19/07.

Further, it is unclear as how to increase ursodeoxycholic acid level in such patient.

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B O'Hara can be reached on (571) 272-0878. The IFW official Fax number is (571) 273-8300.

18. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Patent Examiner
Technology Center 1600
February 1, 2008